Abstract

Epidemiological data suggest that inflammation and innate immunity play significant roles in the pathogenesis of age-related hearing loss (ARHL) in humans. In this mouse study, real-time RT-PCR array targeting 84 immune-related genes revealed that the expressions of 40 genes (47.6%) were differentially regulated with greater than a twofold change in 12-month-old cochleae with ARHL relative to young control mice, 33 (39.3%) of which were upregulated. These differentially regulated genes (DEGs) were involved in functional pathways for cytokine–cytokine receptor interaction, chemokine signaling, TNF signaling, and Toll-like receptor signaling. An NF-κB subunit, *Nfkb1*, was upregulated in aged cochleae, and bioinformatic analyses predicted that NF-κB would interact with the genomic regulatory regions of eight upregulated DEGs, including *Tnf* and *Ptgs2*. In aging cochleae, major proinflammatory molecules, *IL1B* and *IL18rap*, were upregulated by 6 months of age and thereafter. Remarkable upregulations of seven immune-related genes (*Casp1*, *IL18r1*, *IL1B*, *Card9*, *Clec4e*, *Ifit1*, and *Tlr9*) occurred at an advanced stage (between 9 and 12 months of age) of ARHL. Immunohistochemistry analysis of cochlear sections from the 12-month-old mice indicated that IL-18r1 and IL-1B were localized to the spiral ligament, spiral limbus, and organ of Corti. The two NF-κB-interacting inflammatory molecules, TNFα and PTGS2, immunolocalized ubiquitously in cochlear structures, including the lateral wall (the stria vascularis and spiral ligament), in the histological sections of aged cochleae. IBA1-positive

macrophages were observed in the stria vascularis and spiral ligament in aged mice. Therefore, inflammatory and immune reactions are modulated in aged cochlear tissues with ARHL.